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High-dose intravenous melphalan with autologous stem cell transplantation in AL amyloidosis-associated end-stage renal disease

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Background. The development of end-stage renal disease (ESRD) is common among patients with amyloid light-chain AL amyloidosis-associated renal disease and survival of these patients is poor. High-dose intravenous melphalan and autologous stem cell transplantation induce remission of the plasma cell dyscrasia in a significant proportion of patients with AL amyloidosis. The efficacy and tolerability of such treatment for patients with AL amyloidosis-associated ESRD are unknown.

Methods. Between June 1994 and June 2000, 15 patients with AL amyloidosis-associated ESRD were treated with intravenous melphalan (70 to 200 mg/m^2) and autologous peripheral blood stem cell transplantation. Clinical and laboratory data were prospectively collected prior to treatment, during the peritransplant period, and at 3 months, 12 months, and annually thereafter. Treatment outcomes and toxicities were compared with 180 non-ESRD patients treated during the study period.

Results. Eight of 15 patients (53%) had a hematologic complete response following treatment. Two patients (13%) died during the peritransplant period. Transfusion requirements were greater and there was a trend toward increased severity of mucositis in the ESRD patients compared with the non-ESRD patients. Median survival for the ESRD patients with a hematologic complete response was 4.5 years. Five patients with hematologic complete response have either undergone or are awaiting renal transplantation.

Conclusion. High-dose intravenous melphalan with stem cell transplantation is an effective treatment in selected patients with AL amyloidosis-associated ESRD. Although the toxicity profile is greater in ESRD patients, the treatment offers the possibility of successful renal transplantation if hematologic remission is achieved. This treatment should be considered for patients with AL amyloidosis-associated ESRD.

Key words: AL amyloidosis, renal failure, treatment, autologous stem cell transplantation, end-stage renal disease, melphalan.

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AL amyloidosis is a systemic disease characterized by progressive organ dysfunction resulting from the tissue deposition of monoclonal immunoglobulin light chains or light-chain fragments in the form of amyloid fibrils. The kidney is one of the most common sites of amyloid deposition, with clinically evident renal involvement occurring in 48% to 82% of patients [1–5]. Most patients with AL amyloidosis-associated renal disease have nephrotic syndrome, often with massive proteinuria and refractory edema [6]. Renal insufficiency without proteinuria occurs in a subset of patients with isolated tubulointerstitial amyloid deposition. The natural history of amyloidosis-associated renal disease is progressive loss of glomerular filtration rate (GFR) [1, 7]. In a series of 211 patients with AL amyloidosis, one third of those with renal disease at presentation progressed to dialysis dependence [4]. The median time from presentation to initiation of dialysis in these patients was 13.8 months and median survival from the onset of dialysis was 8 months [4].

Cyclic oral melphalan and prednisone has been considered the standard treatment for AL amyloidosis. However, the response to this treatment is unsatisfactory with a median survival of only 16 to 18 months and rare eradication of the plasma cell dyscrasia [3, 5]. At this institution, we have used high-dose intravenous melphalan with autologous peripheral blood stem cell transplantation (HDM/SCT) since 1994 as a more aggressive treatment approach for selected patients with AL amyloidosis. The goal of this treatment is to eliminate the clonal plasma cells producing the amyloidogenic light chains. This treatment has resulted in a hematologic complete response, defined as normal bone marrow biopsy and absence of serum and urine monoclonal protein, in 40% to 50% of patients, a 4-year survival rate of 60%, and clinical improvement in a substantial proportion of surviving patients [8–10]. Among nondialysis-dependent patients with

proteinuria, 71% of those with a hematologic complete response ultimately had a marked reduction in proteinuria [11]. However, because of the toxicity associated with such treatment there has been concern about its utility in patients with end-stage renal disease (ESRD). Other centers have suggested that renal failure is a predictor of poor clinical response to chemotherapy [12], and it has been proposed that AL amyloidosis patients with renal insufficiency are not ideal candidates for myeloablative chemotherapy regimens because of high morbidity and mortality rates [13]. The objective of the present study was to investigate the outcomes of HDM/SCT among patients with AL amyloidosis-associated ESRD.

METHODS

Patients

Approval for the study was obtained from the Institutional Review Board of Boston University Medical Center. All patients with AL amyloidosis-associated ESRD treated with HDM/SCT at Boston University Medical Center between July 1994 and June 2000 were included in this analysis. Requirements for the diagnosis of AL amyloidosis included demonstration of tissue amyloid deposits by Congo Red staining, presence of monoclonal immunoglobulin protein by serum or urine immunofixation electrophoresis, and evidence of clonal plasmacytosis by bone marrow biopsy.

Organ involvement was assessed by a multidisciplinary team that included subspecialists in rheumatology, hematology, nephrology, cardiology, pulmonary, gastroenterology, and neurology. Patients were considered to have AL amyloidosis-associated ESRD if they were dialysis-dependent prior to HDM/SCT, and if renal failure was attributed to amyloidosis based on clinical or histologic findings. Cardiac involvement was defined by septal or posterior wall thickening ≥12 mm by echocardiography in the absence of a history of hypertension or underlying cardiac disease, or by amyloid-related congestive heart failure or arrythmia. Hepatic involvement required the presence of hepatomegaly ≥4 cm below the right costal margin at the midclavicular line by physical examination or serum alkaline phosphatase level ≥2 times the upper limit of normal values. Neurologic involvement was defined as a decrease in systolic blood pressure ≥20 mm Hg with upright posture, gastric atony by gastric emptying scan, symptoms of early satiety, or symptoms or physical examination findings of peripheral neuropathy. Performance status was assessed by two or more clinicians according to the Southwest Oncology Group (SWOG) criteria [14].

Exclusion criteria for HDM/SCT included left ventricular ejection fraction <40%, supine systolic blood pressure <90 mm Hg, oxygen saturation <95% on room air, SWOG performance status ≥3, congestive heart failure or arrhythmias resistant to medical management, and persistent symptomatic pleural effusions. During the study period, 42% of all patients evaluated both met eligibility criteria and elected to undergo treatment with HDM/SCT. Fifteen of 25 patients with ESRD (60%) evaluated during this period underwent treatment with HDM/SCT.

Treatment

Peripheral blood stem cells were mobilized using granular-colony stimulating factor (G-CSF) (Filgrastim; Amgen, Inc., Thousand Oaks, CA, USA), 10 to 16 μg/kg, as the sole mobilizing agent or in combination with granular macrophage-colony stimulating factor (GM-CSF) (Sargamostim, Immunex, Seattle, WA, USA), 250 μg/m^2, as previously described [8, 9]. Melphalan was administered intravenously in divided doses during 2 consecutive days. The total dose of melphalan ranged from 70 to 200 mg/m^2, depending on patient's age, severity of cardiac disease, and performance status. Stem cells were infused 24 to 72 hours after melphalan administration. Hemodialysis patients were dialyzed according to the patient's usual schedule but with an interval of at least 2 hours between either the administration of melphalan or infusion of stem cells and the initiation of hemodialysis. Peritoneal dialysis exchanges were performed according to the patient's usual schedule. Antimicrobial prophylaxis with an oral quinolone and oral acyclovir was started 1 day after stem cell infusion and continued until neutrophil engraftment. A neutrophil count >500/μL for 2 days and platelet count >20,000/μL for 2 days without transfusion in the preceding 48 hours constituted neutrophil and platelet engraftment, respectively. Toxicities were recorded and graded according to National Cancer Institute common toxicity criteria. Treatment was performed in the outpatient setting with hospitalization only if needed for treatment- or disease-related complications.

Evaluations

Patients were evaluated prior to treatment, at 3 and 12 months following treatment, and annually thereafter. At each evaluation, the status of the plasma cell dyscrasia was determined by bone marrow biopsy and immunofixation electrophoresis of serum (SIFE) and urine (UIFE). Hematologic complete response required the absence of detectable monoclonal protein by SIFE and UIFE, as well as bone marrow biopsy with <5% plasma cells and no light-chain predominance. Survival was recorded from the time of treatment, beginning with the first dose of recombinant growth factor for stem cell mobilization. Treatment-related toxicities and blood product requirements were tracked prospectively. The peritransplant period was defined as ≤90 days from the initiation of growth factor administration for stem cell mobilization.

Table 1. Baseline characteristics and organ involvement of end-stage renal disease (ESRD) patients

Patient	Age/sex	Disease duration[a] *months*	Monoclonal light-chain isotype	Dialysis duration *months*	Dialysis modality	SWOG performance status[b]	Predominant organ involvement	Affected organs[c]	Cardiac involvement
1	61/M	24	Lambda	7	PD	1	Kidney	2	+
2	43/M	30	Lambda	7	PD	1	Kidney	1	
3	47/M	19	Lambda	3	PD	2	Kidney	2	+
4	43/F	9	Kappa	7	HD	1	Kidney	1	
5	61/M	11	Lambda	6	PD	1	Kidney	3	
6	50/M	13	Kappa	11	HD	1	Kidney	2	
7	67/F	17	Lambda	0.25	HD	2	Kidney	2	
8	55/F	14	Lambda	4	HD	2	Kidney	1	
9	56/M	5	Lambda	1	HD	2	Heart	3	+
10	55/F	8	Kappa	5	HD	2	Kidney	2	
11	50/F	10	Kappa	32	PD	1	Kidney	1	
12	51/M	19	Lambda	17	HD	2	Kidney	5	+
13	47/F	5	Kappa	3	HD	1	Heart	3	+
14	64/F	21	Kappa	14	HD	2	Kidney	1	
15	40/M	9	Lambda	0.25	HD	2	Kidney	2	

Abbreviations: SWOG, Southwestern Oncology Group; HD, hemodialysis; PD, peritoneal dialysis.
[a] Disease duration is defined from time of tissue diagnosis of amyloidosis
[b] SWOG Performance Status scale: 0 = asymptomatic; 1 = symptomatic, fully ambulatory; 2 = symptomatic, in bed <50% of day; 3 = symptomatic, in bed >50% of day; 4 = bedridden.
[c] Affected organs include kidney, heart, gastrointestinal tract/liver, nervous system, endocrinologic system, and soft tissue

Analysis

Response rates, complication rates, and survival of the 15 patients with ESRD were compared with the 180 patients without ESRD treated during the same period. Comparisons were performed using the Wilcoxon test for continuous variables and Fisher's exact test for categorical variables. Survival curves were generated using the Kaplan-Meier technique and compared using the log-rank test. All analyses used a two-tailed significance value of 0.05 and were performed with NCSS 2001 software (NCSS.com, Kaysville, UT, USA).

RESULTS

Patients

Baseline characteristics of the patients with AL amyloidosis-associated ESRD treated with HDM/SCT are shown in Table 1. The median age of the patients was 51 years, 53% were male, and 60% had a lambda monoclonal protein. The median duration of dialysis-dependence prior to treatment was 7 months and the median time from diagnosis of amyloidosis to treatment was 13 months. Five patients received peritoneal dialysis and the remainder received hemodialysis. The majority of patients had extrarenal amyloid involvement and five patients had symptomatic cardiac disease.

Treatment-related toxicity

Treatment related toxicities for the ESRD patients are shown in Tables 2 and 3. Two patients died within 30 days of beginning stem cell mobilization (patients 9 and 11). One death was due to a ventricular arrhythmia 1 day following stem cell infusion and the other death was a result of respiratory failure 13 days after stem cell infusion. Mucositis occurred in 11 of the ESRD patients. Median mucositis grade in the ESRD group was 2 compared with a median grade of 1 in the non-ESRD patients ($P = 0.09$) and the proportion of patients with grade 3 or 4 mucositis was greater in ESRD patients (43% vs. 20%; $P = 0.05$). Neutropenic fever occurred in 67% of the ESRD patients. Three patients had culture-positive bacteremia, one patient had pneumonia, and one patient had a mucocutaneous herpes simplex virus (HSV) infection. Red blood cell transfusion requirements were greater in ESRD patients (median, 4 units; range, 1 to 24 units) compared with non-ESRD patients (median, 2 units; range, 0 to 35 units; $P = 0.04$). Similarly, the platelet transfusion requirement for the ESRD patients (median, 10 units; range, 0 to 48 units) was greater than that for the non-ESRD patients (median, 4 units; range, 0 to 93 units; $P = 0.03$). Median number of days hospitalized, days to neutrophil engraftment, and days to platelet engraftment did not differ significantly between the ESRD and non-ESRD patients.

Response to treatment and survival

Treatment outcomes for the ESRD patients are shown in Table 4. A hematologic complete response was evident at 12 months in eight of the 11 evaluable patients for an overall hematologic complete response rate of 53%. Performance status was either unchanged or improved following treatment in all surviving patients. With follow-up through February 2002, the median survival for the 15 ESRD patients was 25 months after treatment. Comparison of survival between the ESRD patients and non-ESRD patients is shown in Figure 1. There was not a

Table 2. Treatment toxicities and blood product requirements in the end-stage renal disease (ESRD) patients

Patient	Melphalan *mg/m²*	Mucositis grade 1 to 4	Neutropenic fever	Infection	Gastrointestinal bleed	Hospital days	Red blood cell transfusions *units*	Platelet transfusions *packs*
1	100	0				0	2	0
2	100	4	+	Herpes simplex mucositis		4	6	10
3	100	0				2	1	0
4[a]	100 × 2	3	+			2	2	13
5[a]	100 × 2	1	+			1	4	7
6	200	2	+			8	3	2
7	140	2	+	Bacteremia		6	5	4
8	200	4	+	Bacteremia, multiple infections	+	49	24	48
9[b]	140	NA[c]				1	NA[c]	NA[c]
10	200	4	+	Bacteremia		6	4	18
11[b]	140	0				1	4	10
12	140	3	+			10	13	16
13	200	1				7	3	12
14	70	1	+	Pneumonia		0	11	11
15	200	2	+			5	8	9

[a] Patients 4 and 5 received two courses of treatment with melphalan at 100 mg/m² in a tandem fashion within 12 months
[b] Peritreatment death: Patient 9 died on Day 1 due to ventricular arrhythmia; Patient 11 died on Day 13 due to respiratory failure
[c] NA, not applicable because patient died 1 day following stem cell infusion

Table 3. Treatment-related toxicities in end-stage renal disease (ESRD) and non-ESRD patients

Complication	ESRD[a] *N* = 14	Non-ESRD *N* = 180	*P* value
Red blood cell transfusion *units*	4 (1–24)	2 (0–35)	0.04
Platelet transfusion *units*	10 (0–48)	4 (0–93)	0.03
Hospitalization *days*	4.5 (0–49)	7 (0–60)	0.17
Mucositis grade	2 (0–4)	1 (0–4)	0.09
Mucositis grade 3 or 4 *%*	43	20	0.05
Neutrophil engraftment *days*	11.5 (9–19)	10 (7–17)	0.09
Platelet engraftment *days*	17 (10–39)	14 (0–65)	0.14
Gastrointestinal bleed *%*	7	13	0.7

[a] ESRD patient 11 was excluded from analysis because of death on day 1. For those patients who received two courses of treatment only complications from the first treatment course were analyzed. Continuous variables are presented as medians with range.

statistically significant difference in survival between the two groups.

The small size of the ESRD cohort precludes formal comparisons of outcomes between patients with hematologic complete response and those without. However, it is noteworthy that none of the three patients with persistence of the plasma cell dyscrasia at 12 months survived beyond 2.2 years while six of the eight patients with a hematologic complete response are still alive at a median follow-up of 4.5 years (range, 1.4 to 6.1 years). Four of these six patients received melphalan at a dose of 200 mg/m². Among the patients who did not achieve a hematologic complete response, one (patient 5) died from an anaphylactic reaction to cyclosporine, one (patient 7) died from a hemorrhagic cerebral infarct that was unrelated to amyloidosis, and one (patient 13) died from a cardiac arrhythmia that was related to cardiac amyloidosis. Two patients with hematologic complete response have undergone successful living-related renal transplantation and have well-functioning allografts at 5.3 and 5.4 years after stem cell transplantation. One patient underwent successful cadaveric renal transplantation and has a functioning allograft 6 years after treatment. Two other patients with hematologic complete response are on waiting lists for cadaveric renal transplantation. In the two patients who survived more than 3 months but less than 1 year (i.e, patients not evaluable at 12 months), persistent plasma cell disease was present in one (patient 3) and a hematologic complete response was evident in the other (patient 12) at the 3-month follow-up evaluation.

DISCUSSION

This is the first report detailing the outcomes of dose-intensive melphalan and autologous blood stem cell transplantation in patients with AL amyloidosis-associated ESRD. Eight of the 15 patients (53%) had a complete hematologic response evident 12 months after treatment, and six of these eight patients (75%) are alive at a median follow-up of 4.5 years. The median survival of 25 months for all ESRD patients exceeds the median survival reported in other series for all AL amyloidosis patients treated with oral melphalan and prednisone [3, 5]. Three of the patients have received renal allografts and two patients have been placed by their referring centers on waiting lists for cadaveric renal transplantation.

Median survival in those eight patients with a hematologic complete response at 12 months was 4.5 years compared with survival of 13 to 26 months in the three subjects who did not achieve a hematologic complete response. This association between hematologic outcome and survival is evident in the full cohort of patients treated at this institution as well [10]. Of note, the hematologic com-

Table 4. Treatment outcomes in the end-stage renal disease (ESRD) patients

Patient	Hematologic response at 12 months[a]	Survival status/follow-up	Renal transplantation	Cause of death	Death attributed to amyloid
1	Non-CR	Dead/26 months		Arrhythmia	Yes
2	CR	Alive/73 months	Yes		
3	Not available	Dead/9 months		Sudden death	Yes
4	CR	Alive/65 months	Yes		
5	Non-CR	Dead/13 months		Anaphylaxis to cyclosporine	No
6	CR	Alive/64 months	Yes		
7	CR	Dead/58 months		Hemorrhagic CVA	No
8	Non-CR	Dead/17 months		Pulmonary/renal failure and infection	Yes
9	Not available	Dead/0 months		Arrythmia	Yes
10	CR	Alive/50 months	Waiting list		
11	Not available	Dead/0.4 months		Pulmonary failure	No
12	Not available	Dead/11 months		Sudden death	Yes
13	CR	Dead/17 months		Arrhythmia	Yes
14	CR	Alive/37 months			
15	CR	Alive/34 months	Waiting list		

Abbreviations are: CR, hematologic complete response; Non-CR, hematologic noncomplete response; CVA, cerebrovascular accident.
[a] Classified as "Not available" if death occurred before 1 year

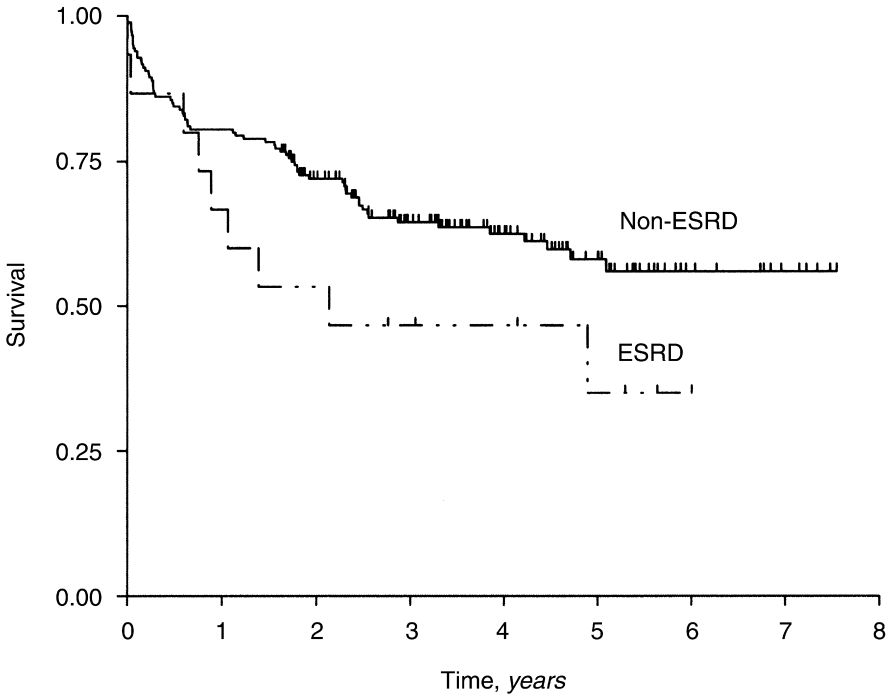

Fig. 1. Survival from time of treatment of end-stage renal disease (ESRD) patients compared with non-ESRD patients ($P = 0.1$ by log-rank test).

plete response rate in the ESRD patients is at least as good as that seen in the full cohort (53% vs. 41%) [10]. Although the small number of ESRD patients studied limits the power for comparisons with the non-ESRD group, a trend toward inferior long-term survival in the ESRD patients is apparent, particularly between the first and second years following treatment (Fig. 1). Such a finding is not unexpected given the negative impact of ESRD on survival in the general population.

High-dose myelosuppressive chemotherapy is associated with significant toxicity that can be particularly severe in patients with AL amyloidosis because of underlying organ dysfunction. Peritransplant mortality rates in AL amyloidosis patients range from 14% to 44% at different institutions [8, 9, 13, 15, 16]. In this series, the peritransplant mortality of 13% is no different than that of the full cohort of 195 patients (14%). Thus, ESRD is not a predictor of increased treatment-related mortality. However, the ESRD patients did have more severe mucositis and an increased requirement for red cell and platelet transfusion support. In previous studies from this institution, symptomatic cardiac disease was found to

be the single most powerful predictor of poor treatment outcome [10]. It is noteworthy that all five of the 15 patients in this series with cardiac disease in addition to ESRD died of cardiac-related complications, although only one of these deaths occurred during the peritransplant period.

One might have predicted that certain treatment complications such as bleeding and infection would be particularly frequent or severe in dialysis patients receiving high-dose chemotherapy. Gastrointestinal bleeding has been reported previously as a complication of dose-intensive chemotherapy in non-ESRD AL amyloidosis patients [10, 15, 16]. Among the 15 ESRD patients in our series, one patient had gastrointestinal bleeding that occurred in the setting of prolonged thromboctyopenia and anemia. None of the ESRD patients had nongastrointestinal bleeding complications. Three patients developed bacteremia during the peritransplant period. None of the bacteremic episodes resulted in loss of permanent hemodialysis access and none of the peritoneal dialysis patients developed peritonitis during the peritransplant period.

Badros et al [17] have evaluated the outcomes of 38 ESRD patients with multiple myeloma treated with high-dose chemotherapy. They found similar hematologic response rates in the ESRD and non-ESRD patients (37% vs. 33%, $P = 0.7$). While mucositis did not occur at a significantly greater rate when analyzed as a dichotomous variable, pulmonary complications and encephalopathy occurred more frequently in the ESRD group. Dialysis dependence had no impact on either overall or event-free survival. Tosi et al [18] have also demonstrated the feasibility of treatment with high-dose cyclophosphamide and autologous stem cell transplantation in six patients with multiple myeloma.

The small size of our cohort of ESRD patients limits the comparisons that can be made between ESRD and non-ESRD patients. In addition, it is important to recognize that our findings cannot be generalized to all patients with AL amyloidosis-associated ESRD, as only those patients meeting the specified eligibility criteria were treated with high-dose melphalan with stem cell transplant. However, although careful patient selection and an experienced multidisciplinary management team may have contributed to the positive outcomes in the current study, it should be noted that one third of the ESRD patients in our series had symptomatic cardiac involvement and one fourth of the patients had more than three organ systems involved. Thus, while the treated cohort may not be fully representative of all patients with AL amyloidosis-associated ESRD, it included those with severe disease manifestations and a range of clinical characteristics.

Renal failure has been viewed as a poor prognostic factor for survival following high-dose chemotherapy, and autologous stem cell transplantation protocols often exclude patients with renal impairment. At present, HDM/SCT appears to be the most effective treatment for AL amyloidosis. Our findings demonstrate that such treatment is tolerable and effective in selected patients with ESRD. We conclude that aggressive treatment with HDM/SCT should be considered for patients with AL amyloidosis-associated ESRD and it would be unjustified to exclude them a priori from such treatment. However, strategies to limit mucositis and minimize infectious complications should be sought to moderate the toxicity of treatment.

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